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The Advance Publication of this article contained an incomplete version of Table 2 and an incorrect table title. The unit of increase in NO<sub>2</sub> was corrected from 10 meta<sup>3</sup> to 10-μg/m<sup>3</sup>. The correct version is shown below.

**Table 2.** Meta-estimates of the association between lung cancer and a 10-μg/m<sup>3</sup> increase in NO<sub>2</sub>

| <b>Estimate</b>            | <b>Meta estimate<br/>(95% CI)</b> | <b>I-squared</b> | <b>Studies Included (by ID)<sup>a</sup></b> |
|----------------------------|-----------------------------------|------------------|---|
| Full Meta Estimate         | 1.04 (1.01, 1.08)                 | 72.8%            | All   |
| Continent                  |                                   |                  |   |
| Europe                     | 1.02 (0.99, 1.06)                 | 41.1%            | 7, 8-13                                     |
| North America              | 1.07 (1.01, 1.14)                 | 77.1%            | 1-6   |
| Asia                       | 1.11 (1.03, 1.20)                 | 32.5%            | 14, 15                                      |
| Exposure Assessment Method |                                   |                  |   |
| Fixed site monitor         | 1.05 (0.98, 1.13)                 | 80.7%            | 1, 2, 4, 8, 12, 14                          |
| Other                      | 1.04 (1.00, 1.08)                 | 60.5%            | 3, 6, 7, 9-11, 13, 15                       |
| Confounder Adjustment      |                                   |                  |   |
| Smoking status             | 1.04 (1.00, 1.08)                 | 71.8%            | 1, 2, 4, 5, 7, 8, 9, 12-15                  |
| SES/income                 | 1.04 (0.98, 1.11)                 | 68.8%            | 4, 6, 7, 9, 11, 13, 15                      |
| Education                  | 1.03 (1.00, 1.07)                 | 68.2%            | 1, 2, 5, 8, 10-12, 13                       |
| Occupation                 | 1.02 (0.99, 1.04)                 | 40.9%            | 2-5, 7, 8, 11, 13                           |

<sup>a</sup>See Table 1 for study ID numbers

# **Lung Cancer and Exposure to Nitrogen Dioxide and Traffic: A Systematic Review and Meta-Analysis**

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**Running head:** Traffic exposure and lung cancer risk

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**Competing financial interests:** We have no competing financial interests to declare.

## Abstract

**Background and objective:** Exposure to traffic-related air pollutants is an important public health issue. Here, we present a systematic review and meta-analysis of research examining the relationship of measures of nitrogen oxides and of various measures of traffic related air pollution exposure with lung cancer.

**Methods:** We conducted random effects meta-analyses of studies examining exposure to NO<sub>2</sub> and NO<sub>x</sub> exposure and lung cancer. We identified 20 studies that met inclusion criteria and provided information necessary to estimate the change in lung cancer per 10 µg/m<sup>3</sup> increase in exposure to measured NO<sub>2</sub>. Further, we qualitatively assess the evidence of association between distance to roadways and traffic volume associated with lung cancer.

**Results:** The meta-estimate for the change in lung cancer associated with a 10 µg/m<sup>3</sup> increase in exposure to NO<sub>2</sub> was 4% (95% CI: 1%, 8%). The meta-estimate for change in lung cancer associated with a 10 µg/m<sup>3</sup> increase in NO<sub>x</sub> was similar and slightly more precise, 3% (95% CI: 1%, 5%). The NO<sub>2</sub> meta-estimate was robust to different confounding adjustment sets as well as the exposure assessment techniques utilized. Trim-and-fill analyses suggest that if publication bias exists the overall meta-estimate is biased away from the null. Forest plots for measures of traffic volume and distance to roadways largely suggest a modest increase in lung cancer risk.

**Conclusion:** We found consistent evidence of a relationship between NO<sub>2</sub> and NO<sub>x</sub>, as proxies for traffic sourced air pollution exposure, with lung cancer. Studies of lung cancer related to residential proximity to roadways also suggest increased risk, which may be due in part to air pollution exposure. The International Agency for Research on Cancer recently classified outdoor air pollution and particulate matter as carcinogenic (Group 1). These meta-analyses support this conclusion, drawing particular attention to traffic sourced air pollution.

## Introduction

Exposure to air pollution from high-density urban traffic is an important public health issue. Traffic related air pollutants are associated with acute health outcomes as well as chronic respiratory and cardiovascular outcomes (Brunekreef et al. 1997; HEI 2010; Hoek et al. 2002; Tonne et al. 2007). Associations of traffic related air pollution with allergies, asthma and respiratory infections have also been demonstrated in children (Brauer et al. 2002) and in both developed and developing nations (Brunekreef et al. 2009). Evaluation of carcinogenicity of traffic based pollutants is complicated by the fact that the diseases are rare and often develop after a significant latency period. Thus, multiple large, long-term observational studies are required to demonstrate evidence of carcinogenicity from traffic related air pollution. A recent systematic review and meta-analysis evaluated the evidence from epidemiology of lung cancer associated with particulate matter exposure (Hamra et al. 2014); importantly, road traffic is an important contributor to urban particulate matter. The evidence supported the recent classification of ambient air pollution and particulate matter as a Group 1 carcinogen by the International Agency for Research on Cancer.

Here, we present a systematic review and meta-analysis of research examining the relationship of measures of nitrogen oxides (measured as nitrogen dioxide, NO<sub>2</sub>, or nitrogen oxides, NO<sub>x</sub>) and of various measures of traffic exposure and lung cancer. In urban settings, NO<sub>2</sub> is often used as a marker for traffic based air pollution, which is a complex mixture of many diverse carcinogens, such as volatile organic compounds, metals, and carbonyls (Brook et al. 2007; Valavanidis et al. 2008). We conducted analyses of studies focused on NO<sub>x</sub> and NO<sub>2</sub>; the latter is a component of the former, but both have been used as markers of traffic exposure in epidemiological research.

We also evaluated studies that use distance from roadways or volume of traffic on nearby roadways, as indicators of exposure to traffic related air pollution (Brook et al. 2007).

## **Methods**

### **Literature search**

We began with a systematic review of the PubMed database using the following search criteria:

(traffic[Title/Abstract] OR Nitrogen dioxide[Title/Abstract] OR NO<sub>2</sub>[Title/Abstract] OR NO<sub>x</sub>[Title/Abstract] OR Nitrogen oxide[Title/Abstract]) AND (lung cancer[Title/Abstract]).

Studies were further required to be human based epidemiologic studies written in English. A previous, similar search conducted by Hamra et al. (2014) did not retrieve relevant studies in non-English languages; therefore, we do not believe the language restriction led to exclusion of informative studies. This search was conducted in January, 2014, and yielded 179 records.

Abstracts from each paper were then reviewed for relevance to the topic of traffic or nitrogen oxide exposure and lung cancer. This review led to 30 studies for initial consideration.

We required abstracts to explicitly provide a quantitative value for change in lung cancer incidence or mortality associated with exposure to nitrogen oxides or other measure of traffic related air pollution or to suggest that such an estimate was provided in the text. Of the initial 30 abstracts examined, 26 provided this information. Further, we only considered studies that used a case-control or cohort design; thus, ecological studies were not included. Finally, where there were multiple studies that considered the same, or highly overlapping, cohorts, we chose the study that had the longest follow-up time and/or the greater number of lung cancer events.

We abstracted estimates of lung cancer associated with three exposure metrics: NO<sub>2</sub>, NO<sub>x</sub> (NO + NO<sub>2</sub>), and volume of/distance to nearest traffic source. Further, we abstracted information on

confounders for which the authors adjusted in their analyses. All studies adjusted for age and gender.

### **Statistical analyses**

For consistency, all study estimates were converted to represent the change in lung cancer incidence or mortality per 10  $\mu\text{g}/\text{m}^3$  exposure to  $\text{NO}_2$  or  $\text{NO}_x$ . All studies that considered  $\text{NO}_x$  used units of  $\mu\text{g}/\text{m}^3$ . Studies of  $\text{NO}_2$  measured exposure in units of  $\mu\text{g}/\text{m}^3$  or parts per billion (ppb). For studies measuring  $\text{NO}_2$  in ppb, we used a conversion factor of 1 ppb = 1.88  $\mu\text{g}/\text{m}^3$ , which is based on ambient pressure of 1 atmosphere and a temperature of 25 degrees Celsius (Vrijheid et al. 2011). We abstracted the effect estimates that were believed to most effectively adjust for confounding (i.e., the least biased effect estimates), which were largely the ‘main models’ discussed by the authors. There did not appear to be issues of overadjustment or potential adjustment for causal intermediates or colliders in any studies. Most studies used a single-pollutant model; when authors used both a single and multi-pollutant model, we chose estimates from the former.

We utilized random effects estimation for our meta-analysis. Unlike fixed effects estimation, random effects methods include an estimate of the percent of the total variance attributable to between study inconsistency, referred to as the  $I^2$  value (DerSimonian and Laird 1986; Higgins et al. 2003; Higgins et al. 2008). One study (Abbey et al. 1999) presented estimates by sex; these estimates were combined with fixed effects estimation and then included in analyses of the overall meta-estimates. This assumes that the stratum specific estimates are collapsible across strata of gender.

Forest and funnel plots were created to provide a visual representation of the distribution of study specific effect estimates. In addition, we conducted trim and fill analyses, which, in the presence of funnel plot asymmetry, re-calculate the meta-estimate based on hypothetical, unobserved studies that would have been necessary to create a symmetrical funnel plot (Duval and Tweedie 2000; Higgins et al. 2008). Finally, we conducted influence analyses, where the meta-estimate is recalculated excluding one study at a time to test if the overall meta-estimate is robust to exclusion of any single study. We did not include formal assessments of study quality. Analyses were conducted using STATA software (v12.1).

## **Results**

### **Studies included**

We identified 20 studies that met our initial inclusion criteria through PubMed and three additional studies through discussion among co-authors or by searching article references (Cao et al. 2011; Hart et al. 2011; Puett et al. 2014). Six of the 23 studies had at least partially overlapping populations; of these, the three judged to be less informative were excluded (Beeson et al. 1998; Jerrett et al. 2013; Vineis et al. 2006). More informative studies are those that have either better information on estimated individual exposure or a greater number of observed lung cancers. Of particular note, while the exposure assessment for an updated ACS-CPS II study was more accurate (Jerrett et al. 2013), we considered a slightly older study that benefits from a much larger sample size (Krewski et al. 2009). The final dataset included 20 studies that met all required criteria for inclusion in our meta-analyses (Abbey et al. 1999; Beelen et al. 2008; Cao et al. 2011; Carey et al. 2013; Cesaroni et al. 2013; Filleul et al. 2005; Hart et al. 2011; Heinrich et al. 2013; Hystad et al. 2013; Katanoda et al. 2011; Krewski et al. 2009; Lipsett et al. 2011; Nafstad et al. 2003; Nyberg et al. 2000; Puett et al. 2014; Raaschou-Nielsen et al. 2010;



Raaschou-Nielsen et al. 2011; Raaschou-Nielsen et al. 2013; Villeneuve et al. 2014; Yorifuji et al. 2013). Table 1 summarizes the 20 studies included in our analyses, and reports mean (SD) of annual, individual exposure to NO<sub>2</sub> or NO<sub>x</sub> in units of mg/m<sup>3</sup> or ppb, depending on what the authors originally reported. Of these studies, 15 and four provide estimates of the change in lung cancer incidence or mortality associated with NO<sub>2</sub> and NO<sub>x</sub>, respectively; Puett et al (2014) provide only information for distance from roadways. Because the ratio of NO<sub>2</sub> to NO<sub>x</sub> is complex, location-specific, and depends upon the time-varying levels of atmospheric oxides, there is no simple conversion factor to estimate the percent of NO<sub>x</sub> represented by NO<sub>2</sub>. We, therefore, summarize meta-estimates from studies of NO<sub>x</sub> separately.

### **NO<sub>2</sub>/NO<sub>x</sub> and lung cancer**

Figure 1 and table 2 summarize the studies examining the change in lung cancer incidence and mortality associated with traffic exposure as measured by NO<sub>2</sub>. The overall meta-estimate of the change in lung cancer incidence or mortality per 10 µg/m<sup>3</sup> increase in exposure is 4% (95%CI: 1%, 8%), with an I<sup>2</sup> estimate of 72.8%. Region specific estimates vary; for Europe, North America, and Japan, the meta-estimates are 2% (95% CI: -1%, 6%), 7% (95% CI: 0%, 14%), and 11% (95% CI: 3%, 20%), respectively. The funnel plot is visually asymmetrical (figure 2). Trim and fill analyses indicate that five hypothetical studies would need to have been observed to create a symmetrical funnel plot; the meta-estimate for the change in lung cancer per 10 µg/m<sup>3</sup> increase in NO<sub>2</sub> recalculated based on inclusion of these unobserved studies was attenuated towards the null, 1% (95% CI: -2%, 5%). A cohort study by of all residents in Oslo Norway aged 51-90 by Naess et al. (2007) met all inclusion criteria but could not be included in our analyses because risk estimates from this study were based on quartiles of exposure. However, we note that the results of that work support an increase in lung cancer risk associated with NO<sub>2</sub>; percent

change in lung cancer mortality associated with a 1 quartile increase in NO<sub>2</sub> for men and women age 51-70 were 7% (95%CI: -3%, 18%) and 23% (95%CI: 10%, 38%) and for men and women age 71-90 were 9% (95% CI: -2%, 20%) and 12% (95%CI: -2%, 27%), respectively (Naess et al. 2007).

The meta-estimate for the change in lung cancer associated with a 10 µg/m<sup>3</sup> increase in measured NO<sub>x</sub> is 3% (95% CI: 1%, 5%), based on five relative risk estimates for lung cancer associated with a 10 µg/m<sup>3</sup> increase in NO<sub>x</sub> derived from four studies: 1.03 (0.99, 1.07) (Cao et al. 2011), 1.08 (1.02, 1.15) (Nafstad et al. 2003), 1.00 (0.98, 1.03) (Raaschou-Nielsen et al. 2013), 1.04 (1.01, 1.08) and 1.00 (0.93, 1.08) (Raaschou-Nielsen et al. 2010). Figure 3 provides a visual summary of these study specific relative risk estimates. The smaller number of risk estimates available does not allow for detailed analyses of sensitivity to confounder adjustment or other subgroup specific analyses. However, it is notable that the meta-estimate for lung cancer associated with NO<sub>x</sub> is similar to that of NO<sub>2</sub>, but slightly more precise.

Table 2 summarizes sensitivity and subgroup analyses for lung cancer associated with measured NO<sub>2</sub>. When restricted to studies that adjusted for confounding due to smoking status, SES/income, education, or occupation, meta-estimates are largely unchanged; point estimates are similar and confidence intervals largely overlap with that of the overall meta-estimate. Further, when we divide studies by the exposure assessment technique used, the meta-estimates are identical, or nearly identical, to the overall meta-estimate, but with slightly different confidence intervals. Influence analyses suggested that no single study influenced the overall meta-estimate (supplemental table S1).

Evidence from studies that consider distance from traffic sources or volume of traffic at roads nearest to residence is summarized in figure 4. Each study uses a unique exposure contrast; thus, we do not provide a meta-estimate of these study specific measures of lung cancer associated with traffic exposure. We only note that many of the estimates reported are either close to or include a null association within the bounds of 95% confidence intervals reported.

## **Discussion**

We provide a systematic review and meta-analyses of the evidence regarding the association of NO<sub>2</sub>, NO<sub>x</sub>, and distance to roadways or volume of vehicles as markers of exposure to traffic based air pollution. The studies that we considered represent many regions of the world and vary by the level of exposure measured, exposure assessment technique, and potential confounders considered. The results of the overall meta-analyses support a relationship between lung cancer and exposure to air pollution from traffic sources.

Analyses stratified by continent suggest the possibility of geographic variability in the magnitude of the relative risk. However, confidence intervals largely overlap, which limits the ability to draw conclusions about heterogeneity. In addition, exposure lags varied in studies from 0 years to 20 years, but were not reported in some studies; we note that Raaschou-Nielsen found no difference in risk estimates when using a 0 year versus a 10 year exposure lag (Raaschou-Nielsen et al. 2010). Trim-and-fill analyses for NO<sub>2</sub> meta-estimates indicated the potential for publication bias, which, if present, would shift results away from the null. In order to obtain the null result suggested by the trim-and-fill analyses, we would need to observe five hypothetical (i.e. unobserved) studies that obtained results that are the inverse of five studies with the largest and least precise risk estimates. Otherwise, the meta-estimate for NO<sub>2</sub> was robust to confounders

considered and methods of exposure assessment used by the authors of each study. We note that no formal assessment of study quality was conducted as part of this meta-analysis.

Epidemiologic evidence alone does not allow us to assess nitrogen oxides as a causative agent in development of lung cancer. Nitrogen oxides are not thought to be carcinogenic agents (Valavanidis et al. 2008). Rather, they serve as a marker for other pollutants formed in high temperature combustion of fossil fuels, a mixture which also includes fine particles. The role of nitrogen oxides as a marker for traffic-related air pollution is most plausible in urban settings, where traffic is often the primary source of NO<sub>x</sub> in the atmosphere and the main source of variability in NO<sub>x</sub> levels. NO<sub>x</sub> is the sum of NO and NO<sub>2</sub>; as NO<sub>2</sub> is a secondary oxidation product of atmospheric reactions involving NO, the latter of which is directly emitted in combustion, NO<sub>x</sub> is considered a better indicator of traffic pollution than is NO<sub>2</sub> alone. As NO<sub>2</sub> is a component of NO<sub>x</sub> and will, therefore, always be present at a lower concentration, one would expect a lower effect estimate for NO<sub>x</sub> (per µg/m<sup>3</sup>) compared to that for NO<sub>2</sub> assuming that either were the true carcinogenic agent in the traffic pollution mixture. Recent studies have shown that NO<sub>x</sub> is highly correlated to combustion by-products, such as volatile organic compounds and carbonyls (Brook et al. 2007; Curren et al. 2006), many of which are known carcinogens. Combustion of fuel from motor vehicles can contribute a significant portion of outdoor air pollution, particularly in urban areas.

Because cancer is an outcome that is believed to develop over many years, exposure modelling that better approximates long-term, individual level exposures may provide more valid estimates of the carcinogenic potential of traffic, or other, air pollution. This is distinct from studies of outcomes with sudden onset; the latter can rely on aggregate measures, such as fixed site monitors and short-term exposure information, because these measures adequately describe

relevant, short term exposure episodes such as high traffic or temperature days (Gram et al. 2003). Even when modelling techniques are used, the residential level exposures assigned to an individual are, at best, an approximation of individual level exposure. Further, each modelling technique will vary in its ability to provide individual level estimates of exposure to pollution. Land use regression, used in four studies considered here, can provide better prediction around major highways where traffic patterns are better known, but not in areas without dense monitoring systems (Jerrett et al. 2005). Alternately, air dispersion models can account for spatiotemporal differences in pollution concentrations, but rely on assumptions that dispersion patterns are Gaussian, which may not be valid (Bellander et al. 2001). Both of these techniques, as well as other spatio-temporal models, attempt to account for within city contrasts that cannot be accounted for with fixed site monitors. In short, all exposure-modelling techniques provide, at best, an approximation of individual exposure. A detailed comparison of the most commonly used exposure assessment techniques was provided by Jerrett et al. 2005. Results of our meta-analyses for NO<sub>2</sub> were robust to stratification by exposure assessment technique; that is, results were nearly identical regardless of whether or not an exposure modelling technique was used in place of fixed site monitors. It is noteworthy that the meta-estimate restricted to exposure modelling techniques was slightly more precise than that obtained from studies using fixed site monitors.

Similarly, risk estimates for distance to traffic or roadways, summarized in figure 2, are crude in that they do not postulate what an individual's exposure at a residence would be from traffic sources. Distance to roadways can be a marker of socio-economic status, the influence of which can be difficult to fully take into account. Also, the exposure measures for which the relative

risks are estimated are inconsistent across studies; thus, it is impossible to summarize them in any quantitatively meaningful way.

A recent meta-analysis showed a strong and consistent association between exposure to particulate matter and lung cancer; the results, as those presented here, were robust to different confounder sets considered, as well as variation in exposure assessment techniques and study locations (Hamra et al. 2014). The current paper considers indicators of exposure to motor vehicle traffic (nitrogen oxides and distance). Vehicle traffic also generates particulate matter, which can also arise from numerous anthropogenic and natural processes outside of traffic. By considering markers of traffic exposure, we hope to provide a better understanding of the association of lung cancer with pollutant mixtures that are characteristic of urban and highly populated environments. The results for NO<sub>x</sub> and NO<sub>2</sub> are compatible with the hypothesis that traffic-related air pollution increases the risk of lung cancer. Further, the IARC has classified exposure to diesel exhaust as a Group I carcinogen (Benbrahim-Tallaa et al. 2012). The results of our meta-analyses are consistent with this previous determination, and provide further support for the carcinogenicity of air pollution.

## References

- Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Beeson WL, et al. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *American Journal of Respiratory and Critical Care Medicine* 159:373-382.
- Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, et al. 2008. Long-term exposure to traffic-related air pollution and lung cancer risk. *Epidemiology* 19:702-710.
- Beeson WL, Abbey DE, Knutsen SF. 1998. Long-term concentrations of ambient air pollutants and incident lung cancer in california adults: Results from the ahsnog study. *Adventist health study on smog. Environmental health perspectives* 106:813-822.
- Bellander T, Berglind N, Gustavsson P, Jonson T, Nyberg F, Pershagen G, et al. 2001. Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in stockholm. *Environ Health Persp* 109:633-639.
- Benbrahim-Tallaa L, Baan RA, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, et al. 2012. Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. *Lancet Oncology* 13:663-664.
- Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A, et al. 2002. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med* 166:1092-1098.
- Brook JR, Burnett RT, Dann TF, Cakmak S, Goldberg MS, Fan XH, et al. 2007. Further interpretation of the acute effect of nitrogen dioxide observed in canadian time-series studies. *Journal of Exposure Science and Environmental Epidemiology* 17:S36-S44.
- Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, van Vliet P. 1997. Air pollution from truck traffic and lung function in children living near motorways. *Epidemiology* 8:298-303.
- Brunekreef B, Stewart AW, Anderson HR, Lai CK, Strachan DP, Pearce N. 2009. Self-reported truck traffic on the street of residence and symptoms of asthma and allergic disease: A global relationship in isaac phase 3. *Environmental health perspectives* 117:1791-1798.

- Cao J, Yang CX, Li JX, Chen RJ, Chen BH, Gu DF, et al. 2011. Association between long-term exposure to outdoor air pollution and mortality in china: A cohort study. *Journal of Hazardous Materials* 186:1594-1600.
- Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR. 2013. Mortality associations with long-term exposure to outdoor air pollution in a national english cohort. *Am J Respir Crit Care Med* 187:1226-1233.
- Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M, et al. 2013. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in rome. *Environmental health perspectives* 121:324-331.
- Curren KC, Dann TF, Wang DK. 2006. Ambient air 1,3-butadiene concentrations in canada (1995-2003): Seasonal, day of week variations, trends, and source influences. *Atmospheric Environment* 40:170-181.
- DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. *Control Clin Trials* 7:177-188.
- Duval S, Tweedie R. 2000. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *Journal of the American Statistical Association* 95:89-98.
- Filleul L, Rondeau V, Vandentorren S, Le Moual N, Cantagrel A, Annesi-Maesano I, et al. 2005. Twenty five year mortality and air pollution: Results from the french paarc survey. *Occup Environ Med* 62:453-460.
- Gram F, Nafstad P, Haheim LL. 2003. Estimating residential air pollution exposure among citizens in oslo 1974-1998 using a geographical information system. *J Environ Monitor* 5:541-546.
- Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, et al. 2014. Outdoor particulate matter exposure and lung cancer: A systematic review and meta-analysis. *Environmental health perspectives* 122:906-911.
- Hart JE, Garshick E, Dockery DW, Smith TJ, Ryan L, Laden F. 2011. Long-term ambient multipollutant exposures and mortality. *Am J Respir Crit Care Med* 183:73-78.
- HEI. 2010. Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects. (Special Report 17). Boston, MA:Health Effects Institute.
- Heinrich J, Thiering E, Rzehak P, Kramer U, Hochadel M, Rauchfuss KM, et al. 2013. Long-term exposure to no2 and pm10 and all-cause and cause-specific mortality in a prospective cohort of women. *Occupational and Environmental Medicine* 70:179-186.



- Higgins JP, Thompson SG, Deeks JJ, Altman DG. 2003. Measuring inconsistency in meta-analyses. *BMJ* 327:557-560.
- Higgins JPT, Green S, Cochrane Collaboration. 2008. *Cochrane handbook for systematic reviews of interventions*. Chichester, England ; Hoboken, NJ:Wiley-Blackwell.
- Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. 2002. Association between mortality and indicators of traffic-related air pollution in the netherlands: A cohort study. *Lancet* 360:1203-1209.
- Hystad P, Demers PA, Johnson KC, Carpiano RM, Brauer M. 2013. Long-term residential exposure to air pollution and lung cancer risk. *Epidemiology* 24:762-772.
- Jerrett M, Arain A, Kanaroglou P, Beckerman B, Potoglou D, Sahuvaroglu T, et al. 2005. A review and evaluation of intraurban air pollution exposure models. *Journal of exposure analysis and environmental epidemiology* 15:185-204.
- Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, et al. 2013. Spatial analysis of air pollution and mortality in california. *Am J Respir Crit Care Med* 188:593-599.
- Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H, et al. 2011. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in japan. *J Epidemiol* 21:132-143.
- Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, et al. 2009. Extended follow-up and spatial analysis of the american cancer society study linking particulate air pollution and mortality. *Res Rep Health Eff Inst*:5-114; discussion 115-136.
- Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, et al. 2011. Long-term exposure to air pollution and cardiorespiratory disease in the california teachers study cohort. *Am J Respir Crit Care Med* 184:828-835.
- Naess O, Nafstad P, Aamodt G, Claussen B, Rosland P. 2007. Relation between concentration of air pollution and cause-specific mortality: Four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in oslo, norway. *Am J Epidemiol* 165:435-443.
- Nafstad P, Haheim LL, Oftedal B, Gram F, Holme I, Hjermann I, et al. 2003. Lung cancer and air pollution: A 27 year follow up of 16 209 norwegian men. *Thorax* 58:1071-1076.

- Nyberg F, Gustavsson P, Jarup L, Bellander T, Berglind N, Jakobsson R, et al. 2000. Urban air pollution and lung cancer in stockholm. *Epidemiology* 11:487-495.
- Puett RC, Hart JE, Yanosky JD, Spiegelman D, Wang M, Fisher JA, et al. 2014. Particulate matter air pollution exposure, distance to road, and incident lung cancer in the nurses' health study cohort. *Environmental health perspectives* 122:926-932.
- Raaschou-Nielsen O, Bak H, Sorensen M, Jensen SS, Ketzel M, Hvidberg M, et al. 2010. Air pollution from traffic and risk for lung cancer in three danish cohorts. *Cancer Epidemiology Biomarkers & Prevention* 19:1284-1291.
- Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Sorensen M, et al. 2011. Lung cancer incidence and long-term exposure to air pollution from traffic. *Environmental health perspectives* 119:860-865.
- Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, et al. 2013. Air pollution and lung cancer incidence in 17 european cohorts: Prospective analyses from the european study of cohorts for air pollution effects (escape). *Lancet Oncology* 14:813-822.
- Tonne C, Melly S, Mittleman M, Coull B, Goldberg R, Schwartz J. 2007. A case-control analysis of exposure to traffic and acute myocardial infarction. *Environmental health perspectives* 115:53-57.
- Valavanidis A, Fiotakis K, Vlachogianni T. 2008. Airborne particulate matter and human health: Toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 26:339-362.
- Villeneuve PJ, Jerrett M, Brenner D, Su J, Chen H, McLaughlin JR. 2014. A case-control study of long-term exposure to ambient volatile organic compounds and lung cancer in toronto, ontario, canada. *American Journal of Epidemiology* 179:443-451.
- Vineis P, Hoek G, Krzyzanowski M, Vigna-Taglianti F, Veglia F, Aioldi L, et al. 2006. Air pollution and risk of lung cancer in a prospective study in europe. *Int J Cancer* 119:169-174.
- Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, et al. 2011. Ambient air pollution and risk of congenital anomalies: A systematic review and meta-analysis. *Environmental health perspectives* 119:598-606.

Yorifuji T, Kashima S, Tsuda T, Ishikawa-Takata K, Ohta T, Tsuruta K, et al. 2013. Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in shizuoka, japan. *Sci Total Environ* 443:397-402.

**Table 1.** Description of cohorts included.

| Region               | Study ID <sup>a</sup> | Reference                                   | No. of Events      | Total population | Study period | Exposure assessment method <sup>b</sup> | Mean (SD) annual, individual exposure <sup>c</sup>   | Study   |
|----------------------|-----------------------|---|--------------------|------------------|--------------|---|--|---|
| <b>North America</b> |                       |   |                    |                  |              |   |  |   |
| California, USA      | 1                     | Abbey et al. 1999                           | 29 (mortality)     | 5,652            | 1977–1992    | Fixed Site Monitor                      |  | Adventist Health Study on Smog (AHSMOG)                         |
| United States        | 2                     | Krewski et al. 2009                         | 16,615 (mortality) | 499, 968         | 1982–2000    | Fixed Site Monitor                      | 27.9 (85.25) ppb   | American Cancer Society Cancer Prevention Study II              |
| United States        | 3                     | Hart et al. 2011                            | 800 (mortality)    | 53,814           | 1985–2000    | Spatio-temporal model                   | 14.2 (7.1) ppb   | Trucking Industry Particle Study (TriPS)                        |
| California, USA      | 4                     | Lipsett et al. 2011                         | 67 (mortality)     | 12,366           | 1997–2005    | inverse distance weighting              | 33.6 (9.6) ppb   | California Teachers Study (women only)                          |
| Canada               | 5                     | Hystad et al. 2013 <sup>de</sup>            | 2,390 (incidence)  | 5,897            | 1994–1997    | Spatio-temporal model                   | 15.4 (9.0) ppb   | National Enhanced Cancer Surveillance System Case-Control study |
| Toronto, Canada      | 6                     | Villeneuve et al. 2014 <sup>d</sup>         | 327 (incidence)    | 752              | 1997–2002    | Land use regression                     | 22.3 (n/r) ppb   | Study of four tertiary care hospitals in Toronto                |
| United States        | n/a                   | Puett et al. 2014 <sup>e</sup>              | 1,648 (incidence)  | 97, 865          | 1998–2010    | Spatio-temporal model                   | n/a  | Nurses' Health Study  |
| <b>Europe</b>        |                       |   |                    |                  |              |   |  |   |
| Stockholm, Sweden    | 7                     | Nyberg et al. 2000 <sup>d</sup>             | 1,042 (incidence)  | 3,406            | 1985–1990    | Air dispersion                          | n/r  | Residents of Stockholm County (1950–1990)                       |
| Oslo, Norway         | n/a                   | Nafstad et al. 2003 <sup>af</sup>           | 418 (incidence)    | 16,209           | 1972–1998    | Air dispersion                          | 10.7 (n/r) µg/m <sup>3</sup>   | Norwegian cancer registry (Oslo, men only)                      |
| France               | 8                     | Filleul et al. 2005                         | 178 (mortality)    | 14,284           | 1974–1998    | Fixed Site Monitor                      | n/r  | Air pollution and chronic respiratory diseases                  |
| Netherlands          | 9                     | Beelen et al. 2008 <sup>e</sup>             | 1,940 (incidence)  | 120,852          | 1986–1997    | Land use regression                     | 36.9 (n/r) µg/m <sup>3</sup>   | Netherlands Cohort study of Diet and Cancer.                    |
| United Kingdom       | 10                    | Carey et al. 2013                           | 5,241 (mortality)  | 830,429          | 2003–2007    | Air dispersion                          | 22.5 (7.4) µg/m <sup>3</sup>   | Clinical Practice Research Datalink                             |
| Italy                | 11                    | Cesaroni et al. 2013 <sup>e</sup>           | 12,208 (mortality) | 1,265,058        | 2001–2010    | Air dispersion                          | 43.6 (8.4) µg/m <sup>3</sup>   | Rome Longitudinal Study   |
| Germany              | 12                    | Heinreich et al. 2013 <sup>e</sup>          | 41 (mortality)     | 4,752            | 1980–2008    | Fixed Site Monitor                      | 39 (n/r) µg/m <sup>3</sup>   | German Women's Health Study                                     |
| Denmark              | n/a                   | Raaschou-Nielsen et al. 2010 <sup>f</sup>   | 679 (incidence)    | 4,160            | 1970–2001    | Spatio-temporal model                   | 37.6 (n/r) µg/m <sup>3</sup>   | Copenhagen City Heart Study; Copenhagen male study              |
| Denmark              | n/a                   | Raaschou-Nielsen et al. 2011 <sup>de</sup>  | 592 (incidence)    | 52,970           | 1993–2006    | Spatio-temporal model                   | 28.3 (n/r) µg/m <sup>3</sup>   | Danish Diet Cancer Health cohort                                |
| European Union       | 13                    | Raaschou-Nielsen et al. 2013 <sup>def</sup> | 2,095 (incidence)  | 312,944          | 1990's       | Land use regression                     | NO <sub>2</sub> : 5.2 (2.5)–59.8 (10.6) µg/m <sup>3</sup> ;<br>NO <sub>x</sub> : 8.7 (5.7)–107.3 (24.3) µg/m <sup>3g</sup> | European Study of Cohorts for Air Pollution Effects (ESCAPE)    |
| <b>Asia</b>          |                       |   |                    |                  |              |   |  |   |
| China                | n/a                   | Cao et al. 2011 <sup>f</sup>                | 624 (mortality)    | 70,947           | 1991–2000    | Fixed Site Monitor                      | 50 (n/r) µg/m <sup>3</sup>   | China National Hypertension follow-up survey                    |
| Japan                | 14                    | Katanoda et al. 2011                        | 421 (mortality)    | 63,520           | 1983–1995    | Fixed Site Monitor                      | 1.2–33.7 ppb <sup>g</sup>  | Three Prefecture Cohort Study                                   |
| Japan                | 15                    | Yorifuji et al. 2013                        | 116 (mortality)    | 13,412           | 1999–2009    | Land use regression                     | 22.0 (15.0) µg/m <sup>3</sup>  | Shizuoka elderly cohort study                                   |

<sup>a</sup>Only studies of NO<sub>2</sub> receive a Study ID to indicate those studies that contributed to the subgroup analyses in Table 2. <sup>b</sup>Studies utilizing land use regression, spatio-temporal, inverse distance weighted, or air dispersion models are more capable of addressing intra-city comparisons of air pollution exposure. This is because they more closely estimate residential exposure to air pollutants. Each technique achieves this goal in a similar but distinct manner: inverse distance weighting accounts for the distance from monitoring sites to the individual's residence, land use regression includes relevant environmental GIS derived variables in regression analyses, spatiotemporal models create air pollutant *surfaces* that vary by space and time using relevant environmental GIS derived variables, and air dispersion models use relevant environmental GIS derived variables but assume that air pollutant transport follows a deterministic process based on Gaussian plume equations. In contrast, fixed site monitors apply single exposure values obtained at monitoring sites to the populations surrounding the monitors, and are most useful for intercity comparisons. <sup>c</sup>n/r indicates that exposure means (SD) were not reported. Nafstad et al. (2003) report the median value of NO<sub>x</sub>. <sup>d</sup>indicates studies that use a case-control design. Unless otherwise noted, all studies are cohort designs. <sup>e</sup>indicates studies that examine lung cancer risk associated with distance to roadways or traffic density. These measures are explicitly described in Figure 2. <sup>f</sup>indicates studies of NO<sub>x</sub>. All other studies examine NO<sub>2</sub> exposure. <sup>g</sup>We report the highest and lowest cohort specific mean (SD) of measured air pollution from Raaschou-Nielsen et al. 2013 among the cohorts pooled for the ESCAPE study. Katanoda et al. 2011 report the range of observed NO<sub>2</sub> values.

**Table 2.** Meta-estimates of the association between lung cancer and a 10-meta<sup>3</sup> increase in NO<sup>2</sup>.

| <b>Estimate</b>            | <b>Meta estimate<br/>(95% CI)</b> | <b>I-squared</b> | <b>Studies Included (by ID)<sup>a</sup></b> |
|----------------------------|-----------------------------------|------------------|---|
| Full Meta Estimate         | 1.04 (1.01, 1.08)                 | 72.8%            | All   |
| Continent                  |                                   |                  |   |
| Europe                     | 1.02 (0.99, 1.06)                 | 41.1%            | 7, 8-13                                     |
| North America              | 1.07 (1.01, 1.14)                 | 77.1%            | 1-6   |
| Asia                       | 1.11 (1.03, 1.20)                 | 32.5%            | 14, 15                                      |
| Exposure Assessment Method |                                   |                  |   |
| Etc.                       | 1.05 (0.98, 1.13)                 | 80.7%            | 1, 2, 4, 8, 12, 14                          |

<sup>a</sup>Study IDs are listed in Table 1.

## Figure Legends

**Figure 1.** Forest plot of study specific estimates of relative risk of lung cancer associated with a  $10 \mu\text{g}/\text{m}^3$  increase in exposure to  $\text{NO}_2$ . The meta-estimate and weights in the forest plot are estimated from random effects meta-analyses.

**Figure 2.** Funnel plot of study specific estimates of the relative risk of lung cancer associated with a  $10 \mu\text{g}/\text{m}^3$  increase in exposure to  $\text{NO}_2$ . \*The meta-estimate represented by the straight, solid line of the funnel plot is based on a fixed effects meta-analysis. Fixed effects meta analysis are required to assess the potential for publication bias, and assumes that there is no between study variation.

**Figure 3.** Forest plot of study specific estimates of relative risk of lung cancer associated with a  $10 \mu\text{g}/\text{m}^3$  increase in exposure to  $\text{NO}_x$ .

**Figure 4.** Relative risk of lung cancer associated with measures of traffic exposure.

Figure 1.

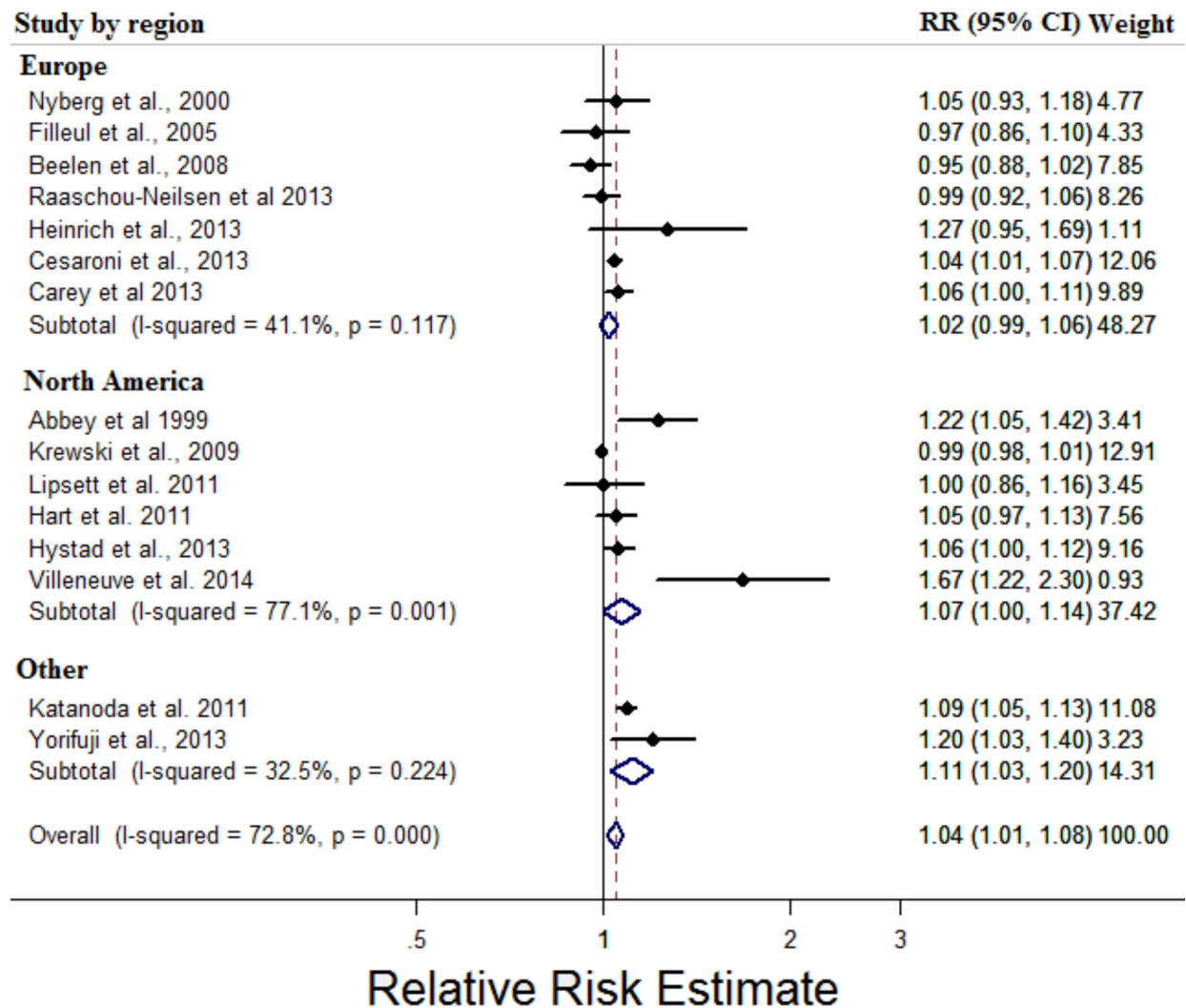


Figure 2.

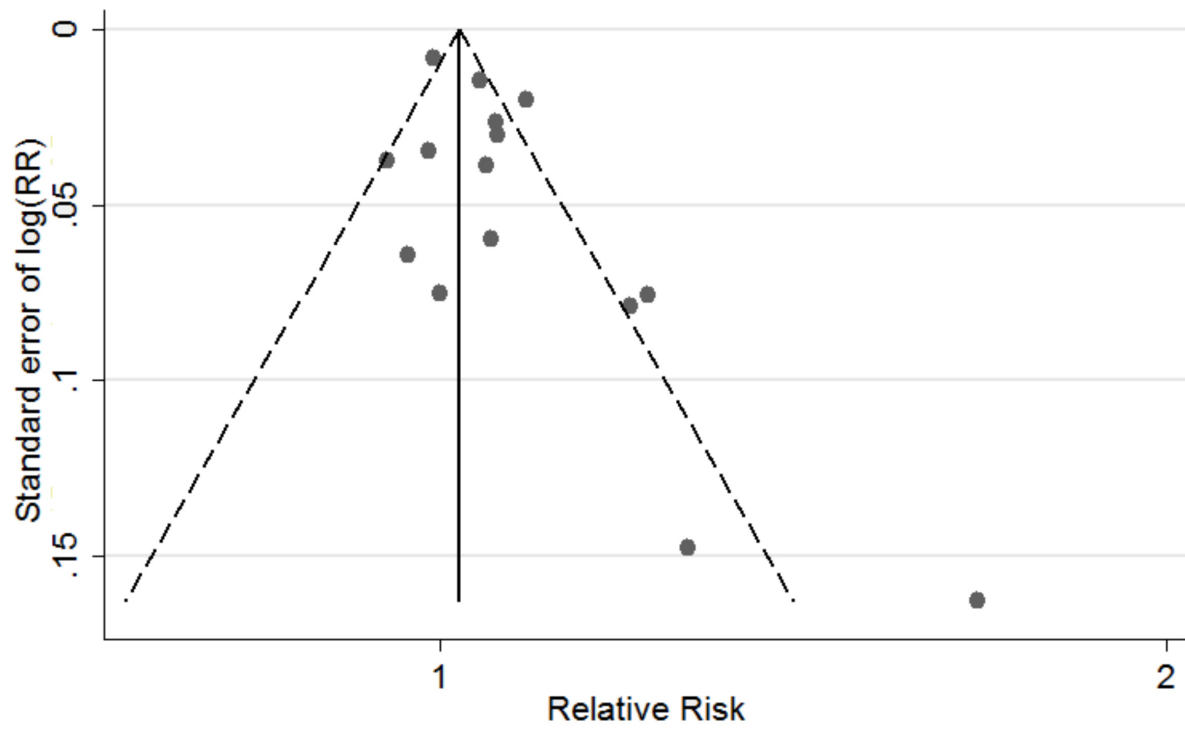




Figure 3.

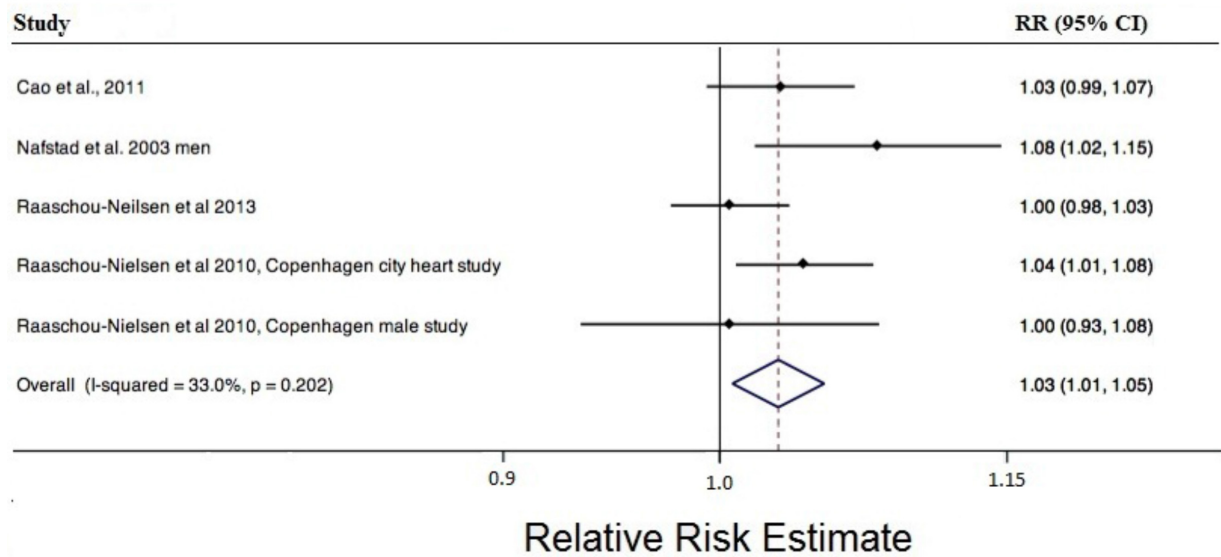


Figure 4.

